

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
15 November 2007 (15.11.2007)

PCT

(10) International Publication Number  
**WO 2007/129111 A1**

(51) International Patent Classification:

*A6IK 31/5513 (2006.01) A6IP 25/24 (2006.01)  
A6IP 5/24 (2006.01) A6IP 25/36 (2006.01)  
A6IP 25/00 (2006.01) A6IP 27/06 (2006.01)  
A6IP 25/18 (2006.01) A6IP 29/00 (2006.01)  
A6IP 25/22 (2006.01)*

(74) Agent: BUCHAN, Gavin MacNicol; European Patent Department, Hoddesdon, Hertfordshire EN11 9BU (GB).

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(21) International Application Number:

PCT/GB2007/050224

(22) International Filing Date: 30 April 2007 (30.04.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

0608655.7 3 May 2006 (03.05.2006) GB

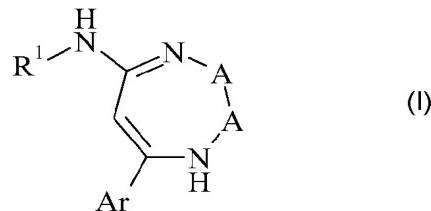
(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: DIAZEPINE DERIVATIVES AS 5-HT<sub>2A</sub> ANTAGONISTS



(57) Abstract: Compounds of formula I: are selective 5HT<sub>2A</sub> antagonists and hence find use in treatment or prevention of a variety of CNS disorders.

WO 2007/129111 A1

## DIAZEPINE DERIVATIVES AS 5-HT<sub>2A</sub> ANTAGONISTS

The present invention relates to a class of diazepine derivatives which act on serotonin receptors (also known as 5-hydroxytryptamine or 5-HT receptors). More particularly, the 5 invention concerns a class of 5-amino-7-aryl-2,3-dihydro-1H-1,4-diazepines and benzo-fused analogues thereof. These compounds are potent and selective antagonists of the human 5-HT<sub>2A</sub> receptor and are therefore useful as pharmaceutical agents, especially in the treatment and/or prevention of adverse conditions of the central nervous system, including sleep disorders such as insomnia, psychotic disorders such as schizophrenia and psychiatric disorders such as anxiety.

10 Compounds of the invention typically display more effective binding to the human 5-HT<sub>2A</sub> receptor than to other human receptors such as D<sub>2</sub> and IKr receptors. They can therefore be expected to manifest fewer side-effects than compounds which do not discriminate in their binding affinity between such receptors. In particular these compounds have lower effects on the IKr receptors and there is a separation of the desired effect from side effects such as cardiac effects.

15 By virtue of their potent human 5-HT<sub>2A</sub> receptor antagonist activity, the compounds of the present invention are effective in the treatment of neurological conditions including sleep disorders such as insomnia, psychotic disorders such as schizophrenia, and also depression, anxiety, panic disorder, obsessive-compulsive disorder, pain, eating disorders such as anorexia nervosa, and dependency or acute toxicity associated with narcotic agents such as LSD or 20 MDMA; and moreover are beneficial in controlling the extrapyramidal symptoms associated with the administration of neuroleptic agents. They are also effective in the lowering of intraocular pressure and hence in treating glaucoma, and may also be effective in treating menopausal symptoms, in particular hot flushes (see Waldinger et al, *Maturitas*, 2000, **36**, 165-8).

25 Various classes of compounds have been disclosed as 5-HT<sub>2A</sub> receptor antagonists, many containing *inter alia* a sulphonyl moiety as described in WO 2005/047246, WO 2005/047247, WO 03/099786, WO 2004/101518, WO 01/74797, WO 00/43362, WO 96/35666, EP-A-0261688, EP-0304888, and US Patents 4,218,455 and 4,128,552, DE-A-3901735 and Fletcher *et al*, *J. Med. Chem.*, 2002, **45**, 492-503. None of these publications, however, discloses or suggests the class of compounds provided by the present invention.

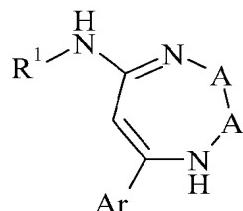
30 US 4,096,140 discloses certain 5-amino-7-aryl-2,3-dihydro-1H-1,4-diazepines as anti-obesity or anti-diabetic agents, but there is no disclosure of activity towards the 5-HT<sub>2A</sub> receptor or of utility in treating conditions known to be mediated by 5-HT<sub>2A</sub> receptor activity.

35 The compounds according to the present invention are potent and selective 5-HT<sub>2A</sub> receptor antagonists, suitably having a human 5-HT<sub>2A</sub> receptor binding affinity (K<sub>i</sub>) of 1000 nM or less, typically of 500 nM or less and preferably of 100 nM or less. The compounds of the invention may possess at least a 10-fold selective affinity, suitably at least a 20-fold selective affinity and preferably at least a 50-fold selective affinity, for the human 5-HT<sub>2A</sub> receptor relative

- 2 -

to the human dopamine D<sub>2</sub> receptor and/or the human IKr receptors. Many compounds also show selectivity relative to the human 5-HT<sub>2c</sub> receptor.

According to the invention there is provided the use, for the manufacture of a medicament for treatment or prevention of a condition mediated by 5-HT<sub>2A</sub> receptor activity, of a compound  
5 of formula I:



I

or a pharmaceutically acceptable salt or hydrate thereof; wherein

each A represents CR<sub>2</sub> where each R is independently H or C<sub>1-4</sub>alkyl, or the moiety A-A  
10 represents 1,2-phenylene;

Ar represents phenyl or pyridyl which bears 0 – 3 substituents selected from halogen, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, CN and CF<sub>3</sub>; and

R<sup>1</sup> represents a hydrocarbon group of up to 12 carbon atoms.

The invention further provides a method of treatment of a subject suffering from or prone  
15 to a condition mediated by 5-HT<sub>2A</sub> receptor activity which comprises administering to that subject an effective amount of a compound according to formula I or a pharmaceutically acceptable salt thereof.

In one aspect of the invention, the condition mediated by 5-HT<sub>2A</sub> receptor activity is sleep disorder, in particular insomnia. In a further aspect of the invention, the condition mediated by 5-HT<sub>2A</sub> receptor activity is selected from psychotic disorders (such as schizophrenia), depression, anxiety, panic disorder, obsessive-compulsive disorder, pain, glaucoma, eating disorders (such as anorexia nervosa), dependency or acute toxicity associated with narcotic agents such as LSD or MDMA, and hot flushes associated with the menopause.

Where a variable occurs more than once in formula I or in a substituent group thereof, the  
25 individual occurrences of that variable are independent of each other, unless otherwise specified.

As used herein, the expression “hydrocarbon group” refers to groups consisting solely of carbon and hydrogen atoms. Such groups may comprise linear, branched or cyclic structures, singly or in any combination consistent with the indicated maximum number of carbon atoms, and may be saturated or unsaturated, including aromatic when the indicated maximum number of  
30 carbon atoms so permits unless otherwise indicated.

As used herein, the expression “C<sub>1-x</sub>alkyl” where x is an integer greater than 1 refers to straight-chained and branched alkyl groups wherein the number of constituent carbon atoms is in the range 1 to x. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl and t-butyl. Derived expressions such as "C<sub>1-4</sub>alkoxy" are to be construed in an analogous manner.

- 3 -

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, of which fluorine and chlorine are preferred and fluorine particularly preferred.

The expression " $C_{3-6}$ cycloalkyl" as used herein refers to nonaromatic monocyclic hydrocarbon ring systems comprising from 3 to 6 ring atoms. Examples include cyclopropyl,  
5 cyclobutyl, cyclopentyl, cyclohexyl and cyclohexenyl.

For use in medicine, the compounds of formula I may be in the form of pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds of formula I or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed  
10 by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, benzenesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid.

When the compounds according to the invention have one or more asymmetric centres,  
15 they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereto in any proportion are encompassed within the scope of the present invention.

When the compounds of formula I have two or more tautomeric forms, it is to be  
20 understood that all such tautomeric forms and mixtures thereof in any proportion are encompassed within the scope of the present invention. For example, the invention extends to the use of tautomers of the compounds of formula I in which the ring nitrogen adjacent to the attachment point of  $R^1NH$  is protonated instead of the ring nitrogen adjacent to the attachment point of Ar.

25 In one embodiment, each A in formula I represents  $CR_2$  where each R is independently H or  $C_{1-4}$ alkyl (such as methyl). In an alternative embodiment the moiety A – A represents 1,2-phenylene (i.e. A – A completes a fused benzene ring). Typically, A – A represents  $CH_2-CH_2$  or 1,2-phenylene, most suitably  $CH_2-CH_2$ .

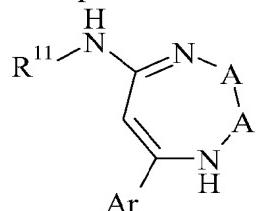
Ar represents phenyl or pyridyl which optionally bears up to 3 substituents selected from halogen,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, CN and  $CF_3$ . In a particular embodiment Ar represents optionally substituted phenyl. Typically, Ar bears not more than 2 substituents. Preferred substituents include halogen (especially Cl and F) and  $C_{1-4}$ alkyl (such as methyl). Specific examples of groups represented by Ar include phenyl, 4-methoxyphenyl, 2-methylphenyl, 4-methylphenyl, 2,4-dimethylphenyl, 3-(trifluoromethyl)phenyl, 2-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl,  
35 2,6-difluorophenyl, 2-fluoro-4-methylphenyl, 2-chlorophenyl, 4-chlorophenyl, 4-cyanophenyl and 2-pyridyl.

$R^1$  represents a hydrocarbon group of up to 12 carbon atoms, preferably of 3 to 10 carbon atoms. Suitable hydrocarbon groups include alkyl groups, in particular branched alkyl groups

- 4 -

such as t-butyl, 2,2-dimethylpropyl, 3-methyl-3-pentyl, 3-ethyl-3-pentyl and 2,3-dimethyl-2-butyl; cycloalkyl groups such as cyclohexyl; alkylcycloalkyl groups such as 1-methylcyclohexyl and 1-ethylcyclopentyl; cycloalkylalkyl groups such as 2-cyclobutyl-2-propyl; and arylalkyl groups such as benzyl, 2-phenylethyl and 2-methyl-3-phenyl-2-propyl.

5 The invention further extends to compounds of formula II:



II

or a pharmaceutically acceptable salt or hydrate thereof; wherein

R¹¹ has the same definition and particular identities as described for R¹ with the proviso  
10 that if R¹¹ represents an alkyl group said alkyl group is branched and comprises at least 5 carbon atoms; and

A and Ar have the same definitions and particular identities as before.

The invention provides pharmaceutical compositions comprising one or more compounds of formula II or pharmaceutically acceptable salts or hydrates thereof and a pharmaceutically acceptable carrier.  
15

The present invention also provides a compound of formula II or a pharmaceutically acceptable salt or hydrate thereof for use in a method of treatment of the human body. Preferably the treatment is for a condition mediated by 5-HT<sub>2A</sub> receptor activity.

Specific compounds useful in this invention include those compounds exemplified  
20 hereinafter and their pharmaceutically acceptable salts.

The compounds of formula I have an activity as antagonists of the human 5-HT<sub>2A</sub> receptor and hence find use in the treatment or prevention of disorders mediated by 5-HT<sub>2A</sub> receptor activity.

The compounds useful in the invention are typically used in the form of pharmaceutical compositions comprising one or more compounds of formula I and a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, transdermal patches, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation.  
25

30 The principal active ingredient typically is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate and dicalcium phosphate, or gums, dispersing agents, suspending agents or surfactants such as sorbitan monooleate and polyethylene glycol, and other pharmaceutical diluents, e.g. water, to form a homogeneous preformulation composition containing a compound of the present

invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This preformulation composition is 5 then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Typical unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. Tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner 10 dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such 15 materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, liquid- or gel-filled capsules, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil or coconut oil, as well as elixirs and similar pharmaceutical 20 vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, poly(ethylene glycol), poly(vinylpyrrolidone) or gelatin.

In the treatment envisaged herein, for example of insomnia or schizophrenia, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and 25 especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day but preferably once per day, for example before going to bed.

If desired, the compounds according to this invention may be co-administered with another sleep inducing or anti-schizophrenic or anxiolytic medicament. Such co-administration may be desirable where a patient is already established on sleep inducing or anti-schizophrenic or 30 anxiolytic treatment regime involving other conventional medicaments. In particular, for the treatment of sleep disorders, the compounds of the invention may be co-administered with a GABA<sub>A</sub> receptor agonist such as gaboxadol, or with a short term and/or rapid-onset hypnotic such as zolpidem, or a benzodiazepine, a barbiturate, a prokinetic modulator, an antihistamine, trazodone, or derivative of trazodone as disclosed in WO 03/068148.

According to a further aspect of the invention, there is provided the combination of a 35 compound of formula I or a pharmaceutically acceptable salt or hydrate thereof and gaboxadol for use in treatment or prevention of sleep disorders, schizophrenia or depression.

- 6 -

Also according to the invention, there is provided a method of treatment or prevention of sleep disorders, schizophrenia or depression comprising administering to a subject in need thereof a compound of formula I or a pharmaceutically acceptable salt or hydrate thereof in combination with gaboxadol.

As used herein, the expression "in combination with" requires that therapeutically effective amounts of both a compound of formula I or a pharmaceutically acceptable salt or hydrate thereof and gaboxadol are administered to the subject, but places no restriction on the manner in which this is achieved. Thus, the two species may be combined in a single dosage form for simultaneous administration to the subject, or may be provided in separate dosage forms for simultaneous or sequential administration to the subject. Sequential administration may be close in time or remote in time, e.g. one species administered in the morning and the other in the evening. The separate species may be administered at the same frequency or at different frequencies, e.g. one species once a day and the other two or more times a day. The separate species may be administered by the same route or by different routes, e.g. one species orally and the other parenterally, although oral administration of both species is preferred, where possible.

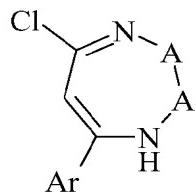
According to a further aspect of the invention there is provided a pharmaceutical composition comprising, in a pharmaceutically acceptable carrier, a compound of formula I or a pharmaceutically acceptable salt or hydrate thereof and gaboxadol.

The invention further provides the use, for the manufacture of a medicament for treatment or prevention of sleep disorders, schizophrenia or depression, of a compound of formula I or a pharmaceutically acceptable salt or hydrate thereof and gaboxadol.

The invention further provides a kit comprising a first medicament comprising a compound of formula I or a pharmaceutically acceptable salt or hydrate thereof and a second medicament comprising gaboxadol together with instructions for administering said medicaments sequentially or simultaneously to a patient suffering from a sleep disorder, schizophrenia or depression.

As used herein, the term "gaboxadol" is inclusive of 4,5,6,7-tetrahydroisoxazolo[5,4-*c*]pyridin-3-ol in free base or zwitterionic form and also of pharmaceutically acceptable acid addition salts thereof such as the hydrochloride salt. Most suitably, gaboxadol is in the form of a crystalline monohydrate of the zwitterionic form.

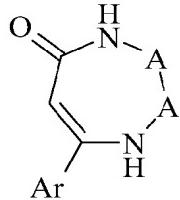
Compounds of formula I may be prepared by the methods disclosed in US 4,096,140, or adaptations thereof. Thus, compounds of formula I may be obtained by reacting amines R<sup>1</sup>-NH<sub>2</sub> with chlorides (1):



- 7 -

where R<sup>1</sup>, Ar and A have the same meanings as before. The reaction takes place at ambient temperature using neat reagents.

Chlorides (1) are available by reaction of POCl<sub>3</sub> with lactams (2):

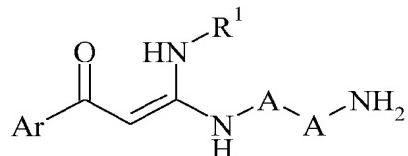


(2)

5

where Ar and A have the same meanings as before. The reaction may be carried out by heating at about 120°C for 12 hours.

Lactams (2) maybe obtained by cyclisation of enamine derivatives (3) in which R<sup>1</sup> is t-butyl:



(3)

10

wherein Ar and A have the same meanings as before. The cyclisation may be effected by refluxing in xylene for 3 hours.

Alternatively, compounds of formula I are conveniently obtained by cyclising compounds 15 (3) under dehydrating conditions, e.g. in the presence of anhydrous CaCl<sub>2</sub> (especially when A-A is 1,2-phenylene) or of strong acid such as perchloric acid or methanesulfonic acid.

Details of these processes, and of the preparation of compounds (3), are disclosed in US 4,096,140 and in the Examples section herein.

Where they are not themselves commercially available, the starting materials and reagents 20 described above may be obtained from commercially available precursors by means of well known synthetic procedures and/or the methods disclosed in the Examples section herein.

It will be appreciated that any compound of formula I initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further desired compound of formula I using techniques known from the art. For example, a bromo substituent 25 present on Ar may be replaced by cyano by treatment with copper(I) cyanide in the presence of 1-methyl-2-pyrrolidinone (NMP).

Where the above-described processes for the preparation of the compounds of use in the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared in racemic 30 form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The compounds may, for example, be resolved into their component enantiomers by standard techniques such as preparative HPLC, or the formation of diastereomeric pairs by salt

- 8 -

formation with an optically active acid, such as di-*p*-toluoyl-D-tartaric acid and/or di-*p*-toluoyl-L-tartaric acid, followed by fractional crystallization and regeneration of the free base. The compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

5 During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may  
10 be removed at a convenient subsequent stage using methods known from the art.

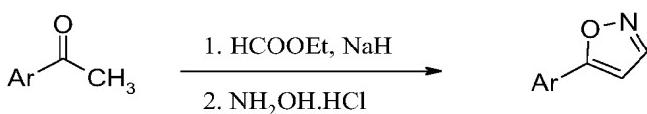
Compounds were tested for their binding to the 5-HT<sub>2A</sub> receptor and to other receptors such as 5-HT<sub>2C</sub> and IKr using the methodology described in Fletcher *et al*, *J. Med. Chem.*, 2002, **45**, 492-503.

15

## EXAMPLES

### General Procedure 1

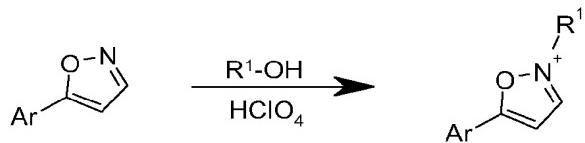
#### Step 1



20

To a stirred mixture of sodium hydride (60%, 14.6g, 385.4mmol), ethyl formate (43.8g, 730.8mmol), and tetrahydrofuran (300 mL) was added the appropriate acetophenone (182.7 mmol) in tetrahydrofuran (100mL) at 0°C. The reaction mixture was stirred for 2.5 h at room temperature, and then diluted with water (200ml) and washed with ethyl acetate. The aqueous layer was separated and hydroxylamine hydrochloride (12.7g, 182.7 mmol) was added. The mixture was stirred for 17 h at room temperature, and then diluted with 1 N HCl and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated to give a yellow solid. The crude solid was recrystallized from diethyl ether to give product as a light yellow powder. Yield: 49-55%.

#### Step 2

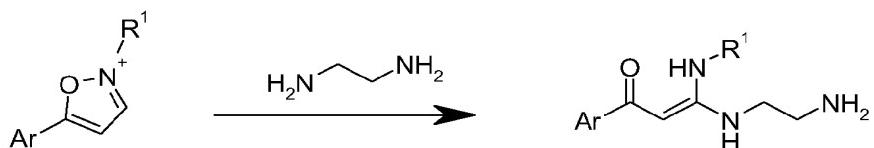


A mixture of the isoxazole from Step 1 (57.5mmol) and the desired alcohol R<sup>1</sup>OH (60mmol) was stirred in an ice bath, and 0.30 mole of 71% perchloric acid was added dropwise. A white precipitate formed during the addition. When all the acid had been added, the precipitate

- 9 -

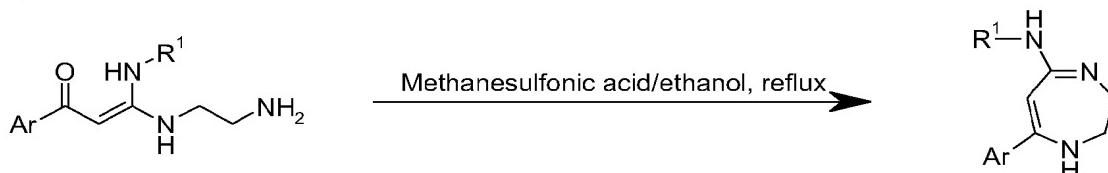
gradually thickened as stirring was continued. About 100 mL of water was added. The suspension was stirred until homogeneous, and the solid was filtered. Washing with water, air drying, and washing with dichloromethane left the crude perchlorate salt. Precipitation from 300 ml of acetonitrile with 600 ml of ether gave colorless rods. Yield: 80-90%.

5 Step 3



To ethylenediamine (16 ml, 240 mmol) in 200 ml of methylene chloride was added 48 mmol of the isoxazolium salt from Step 2 in small portions with stirring over a period of 20 minutes. The temperature of the reaction mixture was maintained at 20-30°C by cooling and stirring was continued for one hour after the addition of the isoxazolium salt. The reaction mixture was diluted to 500ml by addition of methylene chloride, then extracted twice with 300 ml portions of water and dried over anhydrous magnesium sulfate. The methylene chloride was stripped off at a reduced pressure to obtain an oil. The oil was dissolved in 300 ml of anhydrous ether and filtered free of white solids. The white solids were washed with a small amount of anhydrous ether and the washings were combined with the filtrate. The combined filtrate and washings were evaporated at a reduced pressure to obtain the product (8-12g) as a colorless oil.

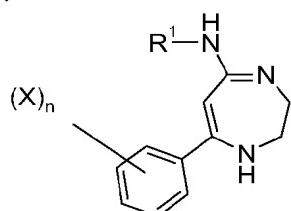
10 Step 4



The product of Step 3 (1 mmol) was dissolved in 5 ml of absolute ethanol. The solution was acidified to a pH of about 1 with methanesulfonic acid, refluxed under nitrogen for one hour, allowed to cool to room temperature and evaporated. The residue was purified by preparative TLC to give the target compound.

Examples 1 - 58

20 25 The following were prepared by the above method, using the appropriate acetophenone in Step 1 and the appropriate alcohol in Step 2:



- 10 -

Example	(X) <sub>n</sub>	R <sup>1</sup>	<sup>1</sup> H NMR (CD <sub>3</sub> OD, 300MHz, δ)
1	H	t-butyl	(*) 7.45~7.57 (s, 1H), 4.95 (s, 1H), 3.31~3.70 (m, 4H), 1.43 (s, 9H).
2	4-OMe	t-butyl	(*) 7.52 (d, <i>J</i> =8.8Hz, 2H), 7.68 (d, <i>J</i> =8.8Hz, 2H), 4.94 (s, 1H), 3.84 (s, 3H), 3.64~3.68 (m, 4H), 1.42 (s, 9H).
3	4-Me	t-butyl	7.48 (d, <i>J</i> =11.2Hz, 2H), 7.26 (d, <i>J</i> =10.4Hz, 2H), 5.0 (s, 1H), 3.58~2.78 (m, 4H), 2.37 (s, 3H), 1.44 (s, 9H).
4	3-CF <sub>3</sub>	t-butyl	7.61~7.87 (m, 4H), 4.99 (s, 1H), 3.68~3.74 (m, 4H), 1.44 (s, 9H)
5	2-F	t-butyl	7.48~7.51 (m, 2H), 7.15~7.30 (m, 2H), 4.80 (s, 1H), 3.70~3.80 (m, 2H), 3.62~3.68 (m, 2H), 1.43 (s, 9H).
6	4-Me	3-Me-3-pentyl	7.35~7.18 (m, 4H), 4.65 (s, 1H), 3.72 (d, <i>J</i> =4.4Hz, 4H), 2.37 (s, 3H), 1.61~1.83 (m, 4H), 1.28 (s, 3H), 0.89 (t, <i>J</i> =9.6Hz, 6H).
7	4-F	t-butyl	7.57~7.62 (m, 2H), 7.18 (t, <i>J</i> =8.7Hz, 2H), 4.82 (s, 1H), 3.65~3.67 (m, 4H), 1.42 (s, 9H).
8	4-F	PhCH <sub>2</sub> C(Me) <sub>2</sub> -	7.56~7.61 (m, 2H), 7.15~7.33 (m, 8H), 4.86 (s, 1H), 3.70~3.73 (m, 4H), 2.67 (s, 2H), 1.40 (s, 6H).
9	2,4-di-Me	PhCH <sub>2</sub> C(Me) <sub>2</sub> -	7.02~7.30 (m, 9H), 4.56 (s, 1H), 3.66~3.77 (m, 4H), 4.56 (s, 1H), 3.66~3.77 (m, 4H), 3.00 (s, 2H), 2.32 (d, <i>J</i> =10.2Hz, 6H), 1.37 (s, 6H).
10	2-Cl	PhCH <sub>2</sub> C(Me) <sub>2</sub> -	7.16~7.47 (m, 9H), 4.59 (s, 1H), 3.68~3.79 (m, 4H), 3.01 (s, 2H), 1.38 (s, 6H).
11	2-Me	3-Me-3-pentyl	7.45 (d, <i>J</i> =8.4Hz, 2H), 7.26 (d, <i>J</i> =4.8Hz, 1H), 4.99 (s, 1H), 3.64 (d, <i>J</i> =4.5Hz, 4H), 3.38 (s, 3H), 1.62~1.86 (m, 4H), 1.30 (s, 3H), 0.91 (t, <i>J</i> =7.5Hz, 6H)
12	2-F	PhCH <sub>2</sub> C(Me) <sub>2</sub> -	7.45~7.60 (m, 2H), 7.17~7.33 (m, 7H), 4.75 (s, 1H), 3.68~3.77 (m, 4H), 3.01 (s, 2H), 1.38 (s, 6H).
13	4-F	3-Me-3-pentyl	7.58~7.63 (m, 2H), 7.19 (t, <i>J</i> =8.7Hz, 2H), 4.97 (s, 1H), 3.64~3.66 (m, 4H), 1.56~1.86 (m, 4H), 1.30 (s, 3H), 0.90 (t, <i>J</i> =10.0Hz, 6H).
14	2,4-di-Me	3-Me-3-pentyl	7.02~7.17 (m, 3H), 4.64 (s, 1H), 3.60~3.70 (m, 4H), 2.30~2.33 (m, 6H), 1.68~1.88 (m, 4H), 1.27 (s, 3H), 0.89 (t, <i>J</i> =7.5Hz, 6H).

- 11 -

Example	(X) <sub>n</sub>	R <sup>1</sup>	<sup>1</sup> H NMR (CD <sub>3</sub> OD, 300MHz, δ)
15	2-Cl	t-butyl	7.39~7.47 (m, 4H), 4.61 (s, 1H), 3.57~3.68 (m, 4H), 4.61 (s, 1H), 3.57~3.68 (m, 4H), 1.40 (s, 9H).
16	2-Me	t-butyl	7.24~7.28 (m, 4H), 4.50 (s, 1H), 3.60~3.80 (m, 4H), 2.37 (s, 3H), 1.40 (s, 9H).
17	2-F	3-Me-3-pentyl	7.45~7.51 (m, 2H), 7.17~7.28 (m, 2H), 4.82 (s, 1H), 3.62~3.70 (m, 4H), 1.62~1.85 (m, 1H), 1.29 (s, 3H), 0.90 (t, J=4.5Hz, 6H).
18	2,4-di-Me	t-butyl	7.07~7.18 (m, 3H), 4.57 (s, 1H), 3.58~3.66 (m, 4H), 2.30~2.33 (m, 6H), 1.39 (s, 9H).
19	2-Cl	3-Me-3-pentyl	7.38~7.51 (m, 4H), 4.88 (s, 1H), 3.63~3.73 (m, 4H), 1.62~1.85 (m, 4H), 1.28 (m, 3H), 0.98 (t, J=7.5Hz, 6H).
20	4-Me	PhCH <sub>2</sub> C(Me) <sub>2</sub> -	(*) 7.44 (d, J=8.4Hz, 2H), 7.22~7.33 (m, 5H), 7.18 (d, J=6.8Hz, 2H), 4.93 (s, 1H), 3.71 (d, J=11.2Hz, 4H), 3.03 (s, 2H), 2.38 (s, 3H), 1.40 (s, 6H).
21	2-F-4-Me	3-Me-3-pentyl	(*) 7.36 (t, J=8.0Hz, 1H), 7.02~7.09 (m, 2H), 4.82 (s, 1H), 3.62~3.68 (m, 4H), 2.38 (s, 3H), 1.75~1.88 (s, 2H), 1.58~1.72 (m, 2H), 1.26 (s, 3H), 0.90 (t, J=7.6Hz, 6H).
22	2-Me	PhCH <sub>2</sub> C(Me) <sub>2</sub> -	(*) 7.17~7.32 (m, 9H), 4.57 (s, 1H), 3.60~3.80 (m, 4H), 3.02 (s, 2H), 2.39 (s, 3H), 1.39 (s, 6H).
23	2-F-4-Me	t-butyl	7.32~7.38 (m, 2H), 7.01~7.08 (m, 2H), 4.76 (s, 1H), 3.67~3.72 (m, 4H), 2.38 (s, 3H), 1.40 (s, 9H).
24	2,4,-di-F	PhCH <sub>2</sub> C(Me) <sub>2</sub> -	7.05~7.56 (m, 1H), 7.22~7.45 (m, 3H), 7.18~7.20 (m, 2H), 7.05~7.18 (m, 2H), 4.72 (s, 1H), 3.68~3.77 (m, 4H), 3.02 (s, 2H), 1.39 (s, 6H).
25	4-CN (***)	3-Me-3-pentyl	7.84 (d, J=8.4Hz, 2H), 7.72 (d, J=8.4Hz, 2H), 4.83 (s, 1H), 3.62~3.72 (m, 4H), 1.63~1.86 (m, 4H), 1.31 (s, 3H), 0.91 (t, J=7.5Hz, 6H).
26	4-CN (***)	PhCH <sub>2</sub> C(Me) <sub>2</sub> -	7.82 (d, J=6.9Hz, 2H), 7.73 (d, J=6.9Hz, 2H), 7.16~7.33 (m, 5H), 3.72~3.78 (m, 4H), 3.03 (s, 2H), 1.40 (s, 6H).
27	2,4-di-F	t-butyl	(*) 7.53~7.55 (m, 1H), 4.77 (s, 1H), 3.64~3.72 (m, 4H), 1.41(m, 9H).
28	2-F	1-Me-cyclohexyl	7.47~7.52 (m, 2H), 7.17~7.29 (m, 2H), 4.86 (s, 1H), 3.62~3.72 (m, 4H), 1.92~1.96 (m, 2H),

- 12 -

Example	(X) <sub>n</sub>	R <sup>1</sup>	<sup>1</sup> H NMR (CD <sub>3</sub> OD, 300MHz, δ)
			1.57~1.60 (m, 8H), 1.33 (s, 3H).
29	2-F	2,3-di-Me-2-butyl	7.45~7.52 (m, 2H), 7.18~7.28 (m, 2H), 4.81 (s, 1H), 3.63~3.73 (m, 4H), 2.21~2.26 (m, 1H), 1.33 (s, 1H), 0.96 (s, 6H).
30	4-F	1-Me-cyclohexyl	7.71~7.76 (m, 2H), 7.30 (t, <i>J</i> =8.7Hz, 2H), 5.11 (s, 1H), 3.76~3.79 (m, 4H), 2.01~2.13 (m, 2H), 1.65~1.78 (m, 5H), 1.52 (s, 3H).
31	4-F	2,3-di-Me-2-butyl	7.60~7.65 (m, 2H), 7.23 (t, <i>J</i> =8.1Hz, 2H), 4.89 (s, 1H), 3.66~3.70 (m, 4H), 2.24~2.28 (m, 1H), 1.36 (s, 6H), 0.98 (s, 6H).
32	4-F	3-Et-3-pentyl	7.59~7.64 (m, 2H), 7.20 (t, <i>J</i> =8.1Hz, 2H), 4.87 (s, 1H), 3.64~3.67 (m, 4H), 1.72 (q, <i>J</i> =7.8Hz, 6H), 0.88 (t, <i>J</i> =7.8Hz, 9H).
33	4-F	1-Et-cyclopentyl	7.58~7.65 (m, 2H), 7.20 (t, <i>J</i> =8.1Hz, 2H), 4.87 (s, 1H), 3.65~3.68 (m, 4H), 1.68~1.88 (m, 8H), 0.91 (t, <i>J</i> =7.2Hz, 3H).
34	2-F-4-Me	PhCH <sub>2</sub> C(Me) <sub>2</sub> -	(*) 7.18~7.40 (m, 6H), 7.02~7.15 (m, 2H), 4.78 (s, 1H), 3.65~3.80 (m, 4H), 3.05 (s, 3H), 2.38 (s, 3H), 1.40 (s, 6H).
35	2-Me	1-Me-cyclohexyl	7.24~7.34 (m, 4H), 4.69 (s, 1H), 3.60~3.80 (m, 4H), 2.40 (s, 3H), 1.93 (m, 2H), 1.50~1.60 (m, 8H), 1.41 (s, 3H).
36	2-Me	1-Et-cyclopentyl	7.21~7.34 (m, 4H), 4.64 (s, 1H), 3.62~3.74 (m, 4H), 2.38 (s, 3H), 1.92~2.12 (m, 2H), 1.65~1.85 (m, 8H), 1.65~1.85 (m, 8H), 0.90 (t, <i>J</i> =7.2Hz, 3H).
37	2,4-di-F	1-Me-cyclohexyl	7.53~7.61 (m, 1H), 7.05~7.14 (m, 2H), 4.89 (m, 1H), 3.65~3.74 (m, 4H), 1.55~1.61 (m, 8H), 1.41 (s, 3H).
38	2,4,-di-F	2,3-di-Me-2-butyl	7.52~7.58 (m, 1H), 7.03~7.11 (m, 2H), 4.81 (s, 1H), 3.62~3.73 (m, 4H), 2.21~2.26 (m, 1H), 1.33 (s, 6H), 0.93~0.96 (m, 6H).
39	2,4-di-F	1-Et-cyclopentyl	7.55 (dd, <i>J</i> =13.8, 8.4Hz, 1H), 7.03~7.12 (m, 2H), 4.80 (s, 1H), 3.63~3.72 (m, 4H), 1.96~2.01 (m, 2H), 1.65~1.82 (m, 8H), 0.90 (t, <i>J</i> =7.5Hz, 3H).
40	2-F	1-Et-cyclopentyl	(*) 7.47~7.52 (m, 2H), 7.19~7.28 (m, 2H), 4.82 (s, 1H), 3.63~3.71 (m, 4H), 1.96~2.02 (m, 2H),

- 13 -

Example	(X) <sub>n</sub>	R <sup>1</sup>	<sup>1</sup> H NMR (CD <sub>3</sub> OD, 300MHz, δ)
			1.74~1.89 (m, 6H), 1.22~1.29 (m, 2H), 0.98~1.19 (m, 3H).
41	2-Me	2,3-di-Me-2-butyl	7.23~7.32 (m, 4H), 4.64 (s, 1H), 3.60~3.80 (m, 4H), 2.37 (s, 3H), 2.20~2.24 (m, 1H), 1.32 (s, 6H), 0.93~0.95 (m, 6H).
42	2,4-di-F	3-Et-3-pentyl	7.51~7.59 (m, 1H), 7.04~7.13 (m, 2H), 4.85 (s, 1H), 3.62~3.71 (m, 4H), 1.68 (t, J=7.5Hz, 6H), 0.85 (t, J=7.5Hz, 9H).
43	2-Me	3-Et-3-pentyl	7.21~7.34 (m, 4H), 4.69 (s, 1H), 3.60~3.78 (m, 4H), 2.35 (s, 3H), 1.62~1.70 (m, 4H), 1.20~1.32 (m, 2H), 0.84~0.89 (m, 9H).
44	2,4-di-F	3-Me-3-pentyl	9.05~9.15 (m, 1H), 8.62~8.65 (m, 2H), 6.43 (s, 1H), 5.15~5.30 (m, 4H), 3.15~3.45 (m, 4H), 2.84~2.94 (m, 3H), 2.44~2.49 (m, 6H).
45	2-F	3-Et-3-pentyl	7.46~7.52 (m, 2H), 7.18~7.28 (m, 2H), 4.86 (s, 1H), 3.63~3.71 (m, 4H), 1.65~1.80 (m, 4H), 1.27~1.37 (m, 1H), 0.83~0.98 (m, 9H).
46	4-Cl	t-butyl	7.45~7.56 (m, 4H), 4.87 (s, 1H), 3.64~3.69 (m, 4H), 1.43 (s, 9H).
47	4-Cl	3-Me-3-pentyl	7.66 (d, J=8.4Hz, 2H), 7.54 (d, J=8.4Hz, 2H), 5.02 (s, 1H), 3.72~3.77 (m, 4H), 1.69~1.98 (m, 4H), 1.46 (s, 3H), 0.98 (t, J=7.2Hz, 6H).
48	4-Cl	PhCH <sub>2</sub> C(Me) <sub>2</sub> -	7.57 (d, J=8.4Hz, 2H), 7.54 (d, J=8.4Hz, 2H), 7.21~7.36 (m, 5H), 4.90 (s, 1H), 3.72~3.78 (m, 4H), 3.07 (s, 3H), 1.43 (s, 6H).
49	4-Cl	1-Me-cyclohexyl	7.58 (d, J=8.4Hz, 2H), 7.56 (d, J=8.4Hz, 2H), 4.87 (s, 1H), 3.64~3.68 (m, 4H), 1.93~1.98 (m, 2H), 1.55~1.61 (m, 8H), 1.40 (s, 3H).
50	4-Cl	2,3-di-Me-2-butyl	7.55 (d, J=8.4Hz, 2H), 7.47 (d, J=8.4Hz, 2H), 4.87 (s, 1H), 3.64~3.68 (m, 4H), 2.12~2.25 (m, 1H), 1.28~1.33 (s, 6H), 0.95 (d, J=6.6Hz, 6H).
51	4-Cl	3-Et-3-pentyl	7.65 (d, J=8.4Hz, 2H), 7.55 (d, J=8.4Hz, 2H), 5.10 (s, 1H), 3.73~3.77 (m, 4H), 1.80 (q, J=7.5Hz, 6H), 0.95 (t, J=7.5Hz, 9H).
52	4-Cl	1-Et-cyclopentyl	7.45~7.58 (m, 4H), 4.81 (s, 1H), 3.55~3.67 (m, 4H), 1.90~2.05 (m, 2H), 1.70~1.88 (m, 7H), 1.55 (m, 1H), 0.91 (t, J=7.2Hz, 3H).

- 14 -

Example	(X) <sub>n</sub>	R <sup>1</sup>	<sup>1</sup> H NMR (CD <sub>3</sub> OD, 300MHz, δ)
53	H (**)	3-Me-3-pentyl	(*) 8.64~8.66 (m, 1H), 7.92~7.95 (m, 2H), 7.50~7.53 (m, 1H), 5.54 (s, 1H), 3.68 (s, 4H), 1.67~1.89 (m, 4H), 1.35 (s, 3H), 0.93 (t, J=7.9Hz, 6H).
54	2-F	2-cyclobutyl-2-propyl	
55	2-Me	2-cyclobutyl-2-propyl	
56	2,4-di-F	2-cyclobutyl-2-propyl	
57	4-Cl	2-cyclobutyl-2-propyl	
58	4-F	2-cyclobutyl-2-propyl	

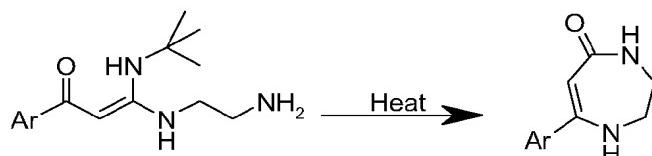
(\*) – 400 MHz

(\*\*) – Ar = 2-pyridyl

(\*\*\*) – prepared from 4-bromo analogue as follows:

To 10 ml of anhydrous dimethylformamide was added 150 mg of bromo derivative and 0.3 g of cuprous cyanide, and the mixture heated under reflux for 6 hours. After cooling, a solution of 1 g of ferric chloride and 1 g of 35 percent hydrochloric acid in 10 ml of water was added and stirred for 20 minutes at 60°C. After cooling to room temperature, the product was extracted twice with 10 ml of CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was washed with water, followed by removing the CH<sub>2</sub>Cl<sub>2</sub>. The resulting solid was purified by preparative TLC to give the target compound.

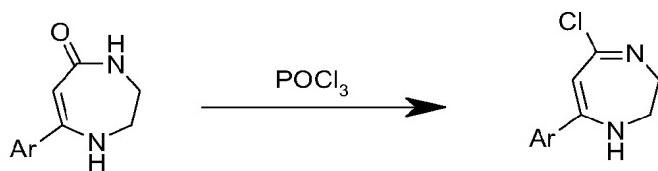
10

**General Procedure 2****Step 1**

The product from General Procedure 1, Step 3 (R<sup>1</sup> = t-butyl) (33.6mmol) in 100 ml of xylene was refluxed under nitrogen for 3 hours. After 30 minutes crystals began to form. The reaction mixture was allowed to cool to room temperature overnight. The crystals that formed were isolated by filtration, washed with xylene and dried to obtain the product (5-8 g) as white crystals.

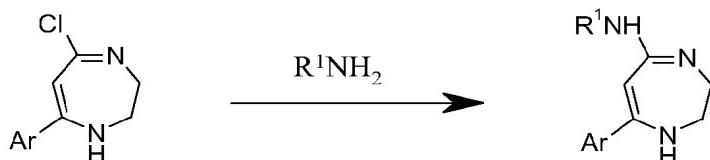
**Step 2**

- 15 -



The lactam from Step 1 (1.2 g) was dissolved in 15 ml of  $\text{POCl}_3$  and heated at  $120^\circ\text{C}$  for 12h. The reaction mixture was allowed to cool and the  $\text{POCl}_3$  was removed at reduced pressure to give the product (1-2 g) in the form of white crystals.

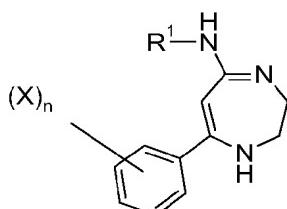
5 Step 3



10

Examples 59 – 65

Using General Procedure 2, the following compounds were prepared:



Example	$(\text{X})_n$	$\text{R}^1$	$^1\text{H NMR} (\text{CD}_3\text{OD}, 400\text{MHz}, \delta)$
59	H	benzyl	7.30~7.58 (m, 10H), 4.86 (s, 1H), 4.42 (s, 2H), 3.63 (s, 4H).
60	H	2,2-di-Me-propyl	7.55~7.60 (m, 3H), 7.43 (d, $J=6.8\text{Hz}$ , 2H), 5.01 (s, 1H), 3.54 (s, 2H), 3.10 (s, 2H), 1.00 (s, 9H).
61	4-Me	bcnzyl	(*) 7.35~7.36 (m, 8H), 4.80 (s, 1H), 4.47 (s, 2H), 3.52 (s, 5H), 2.43 (s, 3H).
62	4-Me	2,2-di-Me-propyl	7.37 (d, $J=8.0\text{Hz}$ , 2H), 7.31 (d, $J=8.0\text{Hz}$ , 2H), 5.00 (s, 1H), 3.55 (s, 4H), 3.09 (s, 4H), 1.02 (s, 9H), 2.43 (s, 3H).
63	H	cyclohexyl	7.51~7.60 (m, 3H), 7.40 (d, $J=7.2\text{Hz}$ , 2H), 4.94 (s, 1H), 3.54 (s, 4H), 3.45 (m, 1H), 2.06 (d, $J=10.8\text{Hz}$ , 2H), 1.83 (d, $J=13.2\text{Hz}$ , 2H),

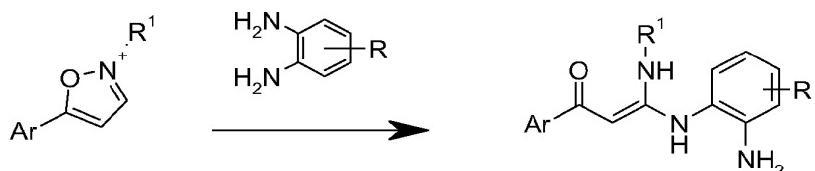
- 16 -

Example	(X) <sub>n</sub>	R <sup>1</sup>	<sup>1</sup> H NMR (CD <sub>3</sub> OD, 400MHz, δ)
			1.22~1.71 (m, 6H).
64	4-Me	cyclohexyl	7.36 (d, <i>J</i> =7.6Hz, 2H), 7.29 (d, <i>J</i> =8.0Hz, 2H), 4.92 (s, 1H), 3.54 (s, 4H), 3.29~3.24 (m, 1H), 2.42 (s, 3H), 2.18~1.95 (m, 2H), 1.86~1.78 (m, 2H), 1.75~1.65 (m, 1H), 1.48~1.18 (m, 5H).
65	2-F	benzyl	(*) 8.60~7.68 (m, 1H), 7.27~7.50 (m, 8H), 4.95 (s, 1H), 4.49 (s, 2H), 3.55 (s, 4H).

(\*) – 300MHz

### General Procedure 3

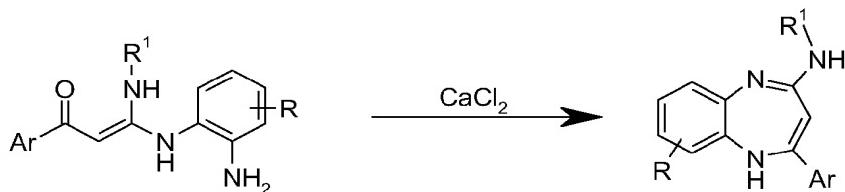
#### Step 1



5

The desired 1,2-phenylenediamine (7.5 mmol) was dissolved in 10 ml of methylene chloride and 1 mmol of isoxazolium perchlorate (General Procedure 1, Step 2) was added to the solution. The temperature of the reaction mixture was maintained at 0°C by cooling. The reaction mixture was diluted by addition of 20 ml of DCM and then extracted twice with 5 ml portions of water and dried over anhydrous magnesium sulfate. The methylene chloride was stripped off at a reduced pressure to give an oil. The oil was dissolved in 5 ml of anhydrous ether and filtered free of white solids. The white solids were washed with a small amount of anhydrous ether and the washings were combined with the filtrate. The combined filtrate and washings were evaporated at a reduced pressure to obtain the product as a colorless oil (1.2~1.5 g, 50~67%). The crude product was directly used to the next reaction without further purification.

#### Step 2

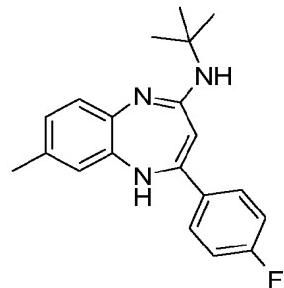


The product of step 1 (1.0 mmol) was dissolved in 5 ml of absolute ethanol. 1.0 g of anhydrous CaCl<sub>2</sub> was added and the solution was stirred under nitrogen for 24 hours. Solid was filtered off and the filtrate concentrated. The residue was recrystallized from DCM/ether to give off-red crystals.

### Example 66

- 17 -

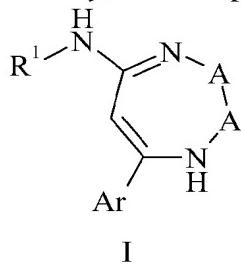
Following General Procedure 3, there was obtained:



<sup>1</sup>H NMR (300MHz, CD<sub>3</sub>OD) δ 7.64~7.69 (m, 2H), 7.25~7.28 (m, 2H), 6.86~6.92 (m, 3H), 4.94 (s, 1H), 2.29 (s, 3H), 1.55 (s, 9H).

**CLAIMS**

1. The use, for the manufacture of a medicament for treatment or prevention of a condition mediated by 5-HT<sub>2A</sub> receptor activity, of a compound of formula I:



5

or a pharmaceutically acceptable salt or hydrate thereof; wherein

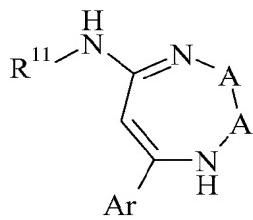
each A represents CR<sub>2</sub> where each R is independently H or C<sub>1-4</sub>alkyl, or the moiety A-A represents 1,2-phenylene;

10 Ar represents phenyl or pyridyl which bears 0 – 3 substituents selected from halogen, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, CN and CF<sub>3</sub>; and

R<sup>1</sup> represents a hydrocarbon group of up to 12 carbon atoms.

2. Use according to claim 1 wherein said condition is selected from sleep disorders, 15 psychotic disorders (such as schizophrenia), depression, anxiety, panic disorder, obsessive-compulsive disorder, pain, glaucoma, eating disorders (such as anorexia nervosa), dependency or acute toxicity associated with narcotic agents such as LSD or MDMA, and hot flushes associated with the menopause.

20 3. A compound of formula II:



II

or a pharmaceutically acceptable salt or hydrate thereof; wherein

25 A and Ar are as defined in claim 1; and

R<sup>11</sup> represents a hydrocarbon group of up to 12 carbon atoms, with the proviso that if R<sup>11</sup> represents an alkyl group said alkyl group is branched and comprises at least 5 carbon atoms.

4. A compound according to claim 3 wherein A-A represents CH<sub>2</sub>-CH<sub>2</sub> or 1,2-30 phenylene.

- 19 -

5. A compound according to claim 3 or claim 4 wherein Ar represents phenyl bearing 0-2 substituents selected from halogen, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, CN and CF<sub>3</sub>.

5 6. A compound according to any of claims 3-5 wherein R<sup>11</sup> is a branched alkyl group comprising 5-12 carbon atoms;

or is selected from cycloalkyl groups, cycloalkylalkyl groups, alkylcycloalkyl groups and arylalkyl groups comprising up to 12 carbon atoms.

10 7. A compound according to claim 6 wherein R<sup>11</sup> is selected from:

2,2-dimethylpropyl, 3-methyl-3-pentyl, 3-ethyl-3-pentyl, 2,3-dimethyl-2-butyl, cyclohexyl, 1-methylcyclohexyl, 1-ethylcyclopentyl, 2-cyclobutyl-2-propyl, benzyl, 2-phenylethyl and 2-methyl-3-phenyl-2-propyl.

15 8. A pharmaceutical composition comprising a compound according to any of claims 3-8 and a pharmaceutically acceptable carrier.

9. A compound according to any of claims 3-8 for use in treatment or prevention of a condition mediated by 5-HT<sub>2A</sub> receptor activity.

20

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/GB2007/050224

A. CLASSIFICATION OF SUBJECT MATTER				
INV.	A61K31/5513	A61P5/24	A61P25/00	A61P25/18
	A61P25/24	A61P25/36	A61P27/06	A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, MEDLINE, EMBASE, BIOSIS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 096 140 A (SIMPSON WILLIAM R) 20 June 1978 (1978-06-20) cited in the application abstract column 1, line 12 - column 2, line 39 claims 1-32	3-6,8,9
A	-----	1-9
X	US 4 315 860 A (SIMPSON WILLIAM R) 16 February 1982 (1982-02-16) abstract column 1, line 17 - column 2, line 39 claims 1-32	3-6,8,9
A	-----	1-9
	-/-	

Further documents are listed in the continuation of Box C.

See patent family annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&\* document member of the same patent family

Date of the actual completion of the international search

31 July 2007

Date of mailing of the international search report

08/08/2007

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Taylor, Mark

## INTERNATIONAL SEARCH REPORT

International application No PCT/GB2007/050224
---

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1 494 433 A (SANDOZ LTD) 7 December 1977 (1977-12-07) abstract page 1, line 11 - line 30 page 3, line 69 - line 86 page 4, line 8 - line 51 claims 1-24 -----	3-6,8,9
A		1-9
P,X	SWAIN ET AL: "Identification and optimisation of 5-amino-7-aryldihydro-1,4-diazepines as 5-HT2A ligands" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 16, no. 23, 7 November 2006 (2006-11-07), pages 6058-6062, XP005850601 ISSN: 0960-894X the whole document -----	1-8

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: -

Present claims 1 and 9 relate to a medical indication which is defined in terms of a given desired property or effect, namely a condition mediated by 5-HT2a receptor activity. However, the description does not provide support and disclosure in the sense of Article 6 and 5 PCT for the unequivocal determination of whether any given condition falls within the scope of this definition, and there is no common general knowledge of this kind available to the person skilled in the art. This non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search of the claim (PCT Guidelines 9.19 and 9.20).

The search of claims 1 and 9 was consequently restricted to the specifically disclosed diseases mentioned in claim 2.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

**INTERNATIONAL SEARCH REPORT**International application No.  
PCT/GB2007/050224**Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
  
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International application No  
PCT/GB2007/050224

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 4096140	A 20-06-1978	AT	355025 B	11-02-1980
		AT	233975 A	15-07-1979
		ES	436126 A1	01-04-1977
		ES	453664 A1	16-11-1977
US 4315860	A 16-02-1982	NONE		
GB 1494433	A 07-12-1977	AU	500509 B2	24-05-1979
		AU	7960175 A	30-09-1976
		CA	1064488 A1	16-10-1979
		CH	613696 A5	15-10-1979
		DE	2512510 A1	02-10-1975
		DK	117975 A	30-09-1975
		ES	453665 A1	16-11-1977
		FI	750827 A	21-09-1975
		FR	2265397 A1	24-10-1975
		IE	40951 B1	12-09-1979
		IL	46958 A	31-07-1978
		JP	51036482 A	27-03-1976
		NL	7503532 A	01-10-1975
		NO	750978 A	30-09-1975
		SE	7503278 A	30-09-1975